

## Chapter 5

# Newborn Screening for MCAD Deficiency



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### What is MCADD?

Medium chain acyl-CoA dehydrogenase deficiency (MCADD), a fatty acid oxidation disorder, is an **autosomal recessive** enzyme deficiency. This condition prevents the normal use of fat as an alternative source of energy during times of fasting or increased metabolic demands. People with MCADD cannot burn fat for energy when their bodies run out of glucose, and as a result they may be affected by low blood sugar, altered central nervous system function, coma, or sudden death.<sup>1, 2</sup> If treatment is initiated before the onset of metabolic crisis, however, morbidity and mortality can be prevented.<sup>1</sup> With an early diagnosis, MCADD can be managed successfully by eating regularly and avoiding fasting.<sup>2</sup>

### Why Test Newborns for MCADD?

Plasma concentrations of MCADD markers in the blood decline significantly after the first few days of life.<sup>3</sup> Because MCADD can be identified more easily during the newborn period, and pre-symptomatic treatment is reported to prevent morbidity and mortality, advocacy groups such as the March of Dimes<sup>2</sup> have recommended universal newborn screening for MCADD.

### Tandem Mass Spectrometry Screening Test

Tandem mass spectrometry (MS/MS) is currently used to screen for MCADD as well as for other metabolic diseases.<sup>4</sup> This method detects elevated levels of certain intermediate metabolites of medium-chain fatty acids that are associated with MCADD. Octanoylcarnitine (C8) is the primary MCADD marker; additional markers include hexanoylcarnitine (C6), decanoylcarnitine (C10), and decenoylcarnitine (C10:1).<sup>3, 5</sup>

The high specificity and sensitivity of MS/MS to identify MCADD have been verified by reported results of newborn screening tests and retrospective MS/MS analyses of specimens from individuals who have been diagnosed clinically. Combined results<sup>5-10</sup> from 1.9 million newborn screening tests contained approximately equal numbers of true-positive (n=112) and false-positive (n=110) MS/MS test results and no known false-negative results.

#### Autosomal Recessive

*Inheritance of two copies of a mutant gene, one from each parent, on one of the 22 autosomes (chromosomes other than X or Y).*



become symptomatic without this screening and subsequent interventions. Identifying affected people who would otherwise remain asymptomatic could subject them to unnecessary medical therapies, psychological stress, and difficulty in obtaining health insurance. Population-based studies to demonstrate the usefulness of MCADD screening have been recommended.<sup>18</sup> CDC and the Health Resources and Services Administration (HRSA) are funding follow-up studies of identified children to increase understanding of the impact of newborn screening for MCADD and other disorders identified by MS/MS.

The potential impact of early identification and intervention for MCADD on mortality is not well understood. Estimated mortality among children clinically diagnosed with MCADD ranges from 8% to 25%.<sup>1,19-21</sup> One study estimated mortality in an unscreened cohort of children with MCADD.<sup>4</sup> This study found eight children with MCADD among 100,600 British children whose stored newborn blood spots were analyzed using MS/MS; one (12.5%) of the eight children with MCADD died. Larger studies of this type or prospective data from screening programs could provide more precise mortality estimates.

The potential impact of newborn screening for MCADD on morbidity is unknown. Long-term neurological impairment has been reported in 16% to 33% of survivors of metabolic crises, about half of whom are seriously impaired.<sup>1,19-21</sup> No cases of neurological impairment in children with MCADD identified by screening programs have been reported.<sup>22-24</sup> Systematic long-term assessment of neurological outcomes is needed; although preliminary data from an assessment of infants born in New England and Pennsylvania indicate normal cognitive development.<sup>24</sup>

### **Cost-Effectiveness of Newborn MCADD Screening**

The two published studies that analyzed cost-effectiveness of adding MS/MS to newborn screening concluded that it is probably cost-effective, either for MCADD alone<sup>9</sup> or because of the added benefits from early detection of disorders in addition to MCADD.<sup>25</sup> A study published in 2003 concluded that, for jurisdictions already using MS/MS to screen for PKU, it would be cost-effective to screen for MCADD as well.<sup>26</sup>

The cost-effectiveness of screening (from the perspective of the screener) using MS/MS depends on the technology chosen and on assumptions about the numbers of lives saved and cases of disability prevented. According to the Wisconsin Public Health Laboratory,<sup>9</sup> the laboratory cost of MS/MS screening for MCADD is about \$4 per infant. The additional costs of confirmatory testing and specialist services for children with MCADD are estimated to add \$1.25 per infant

### Quality-Adjusted Life Years (QALYs)

*Outcome of a treatment measured as the number of years of life saved, adjusted for quality.*

screened. The Wisconsin study estimated a cost-effectiveness ratio of \$42,000 per **quality-adjusted life years (QALYs)** in the base-case analysis, and \$6,000 in the best-estimates analysis. The authors concluded that the true cost-effectiveness ratio is probably below the normal cutoff of \$50,000 per QALY most commonly used to justify healthcare interventions.

### Challenges for Implementing MCADD Screening

The addition of new disorders to newborn screening programs presents many challenges. For MCADD, these may include implementing new technology in the laboratory and assuring appropriate follow-up to confirm the diagnosis of MCADD and begin effective interventions promptly. Legal and ethical issues are also present at every stage of developing and conducting newborn screening programs.

**Laboratory Implementation Issues:** The use of MS/MS has proven to be a reliable method to screen for MCADD. Because plasma concentrations of MCADD markers decline significantly after the first few days of life,<sup>3</sup> it is important to establish age-appropriate cutoff levels for newborn screening tests. CDC's Newborn Screening Quality Assurance Program<sup>27</sup> conducts proficiency testing surveys that have allowed U.S. newborn screening laboratories to meet Clinical Laboratory Improvement Amendments (CLIA) quality assurance (QA) requirements.<sup>28</sup> The surveys include specimens enriched with three MCADD markers—C8, C6, and C10 (no synthetic standard is available for C10:1).

**Follow-Up Implementation Issues:** Short- and long-term follow-up protocols are essential components of newborn screening programs.<sup>29</sup> Several states have developed pilot short- and long-term follow-up studies. For example, Oregon and Iowa are part of a cooperative agreement with CDC to develop a long-term follow-up protocol for MS/MS screening.

**Legal and Ethical Issues:** MS/MS technology used for MCADD screening is able to detect more disorders than those mandated by newborn screening policy, although for many of these disorders, information about the clinical validity or utility of testing is not available. This presents an ethical dilemma that states have approached in various ways. In some states, parents are given the option to consent to receive results of non-mandated tests; other states do not make non-mandated test results available.

### Conclusion

Laboratory testing is only one element of an effective newborn screening program. Clinical follow-up is essential for optimizing outcomes for children and their families. Some states are conducting research that will help fill knowledge gaps related to MS/MS screening for MCADD and other disorders. For example, the

California Department of Health Services instituted a pilot program that lets parents volunteer to have their child undergo supplemental testing for MCADD and other disorders detectable by MS/MS technology. This project aims to generate epidemiological data that will be used to inform policy decisions about which disorders to add to the list of routine screening tests, as well as to evaluate protocols and develop guidelines for follow-up.

## Resources

### General

#### National Newborn Screening and Genetics Resource Center (NNSGRC)

1912 W. Anderson Lane, Ste. 210

Austin, TX 78757

Phone: (512) 454-6419

<http://genes-r-us.uthscsa.edu/index.htm>

#### March of Dimes (MOD)

1275 Mamaroneck Avenue

White Plains, NY 10605

<http://www.modimes.org/>

#### Morbidity and Mortality Weekly Report (MMWR)

April 13, 2001; Vol. 50; No. RR-3

Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns: A Report of a Work Group

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5003a1.htm>

#### Newborn Screening Quality Assurance

In Genetics and Public Health in the 21<sup>st</sup> Century, Khoury MJ et al., editors. Oxford University Press, 2000.

<http://www.cdc.gov/genomics/info/books/21stcent3.htm>

### Tandem Mass Spectrometry

#### Newborn Screening Quality Assurance Program (NSQAP)

[http://www.cdc.gov/nceh/dls/newborn\\_screening.htm](http://www.cdc.gov/nceh/dls/newborn_screening.htm)

### Policy/Legal Issues

#### National Conference of State Legislators (NCSL)

Denver Office:

7700 East First Place

Denver, CO 80230

Tel: 303-364-7700

Fax: 303-364-7800

Washington Office:

444 North Capitol Street, N.W., Suite 515

Washington, D.C. 20001

Tel: 202-624-5400

Fax: 202-737-1069

For information re: genetics laws and legislative activity go to:

<http://www.ncsl.org/programs/health/screen.htm>

## **Ethics**

### **Hastings Center**

Route 9-D / 21 Malcolm Gordon Road

Garrison, NY 10524-5555

Phone: (845) 424-4040

For information re: ethics and newborn screening project go to:

[http://www.thehastingscenter.org/research/prog2/healthcarepolicy\\_4.htm](http://www.thehastingscenter.org/research/prog2/healthcarepolicy_4.htm)

## **References**

1. Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. *Arch Dis Child* May 1999;80: 459-62.
2. March of Dimes Newborn Screening Recommendations. March of Dimes. Available at: [http://www.marchofdimes.com/professionals/580\\_4043.asp](http://www.marchofdimes.com/professionals/580_4043.asp). Accessed Apr 11, 2003.
3. Chace DH, Kalas TA, and Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genomics Hum Genet* 2002;3:17-45.
4. CDC. Using tandem mass spectrometry for metabolic disease screening among newborns. A report of a working group. *MMWR* 2001;50(RR-3):1-23.
5. Pourfarzam M, Morris A, Appleton M, Craft A, Bartlett K. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 2001;358:1063-4.
6. Carpenter K, Wiley V, Sim KG, Heath D, Wilcken B. Evaluation of newborn screening for medium chain acyl-CoA dehydrogenase deficiency in 275,000 babies. *Arch Dis Child Fetal Neonatal Ed* 2001; 85(2):F105-9.
7. Andresen BS, Dobrowolski SF, O'Reilly L, Muenzer J, McCandless SE, Frazier DM, et al. Medium-chain acyl-CoA dehydrogenase (MCAD) mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms: identification and characterization of a new, prevalent mutation that results in mild MCAD deficiency. *Am J Hum Genet* 2001; 68:1408-18.
8. Zytovicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots. *Clin Chem* 2001;47:1945-55.

9. Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. [erratum appears in *J Pediatr* 2003 Jan;142(1):56]. *J Pediatr* 2002;141:524-31.
10. Schulze A, Lindner M, Kohlmuller D, Olgemoller K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003;111:1399-406.
11. Chace DH, Hillman SL, Van Hove JL, Naylor EW. Rapid diagnosis of MCAD deficiency: quantitative analysis of octanoylcarnitine and other acylcarnitines in newborn blood spots by tandem mass spectrometry. *Clin Chem* 1997;43:2106-13.
12. Vreken P, van Lint AE, Bootsma AH, Overmars H, Wanders RJ, van Gennip AH. Quantitative plasma acylcarnitine analysis using electrospray tandem mass spectrometry for the diagnosis of organic acidurias and fatty acid oxidation defects. *J Inher Metab Dis* 1999;22:302-6.
13. Tandem mass spectrometry in newborn screening. American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group. *Genet Med* 2000;2:267-9.
14. National Newborn Screening and Genetics Resource Center. U.S. National Screening Status Report-MS/MS. Web site. Available at: <http://genes-r-us.uthscsa.edu/resources/newborn/msmstests.htm>. Accessed Jan 7, 2004.
15. Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Public Health Rep* 2001;116:122-31.
16. Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, et al. Newborn screening for inborn errors of metabolism: a systematic review. *Health Technol Assess* 1997;1:i-iv,1-95.
17. Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technol Assess* 1997;1:i-iv,1-202.
18. Wang SS, Fernhoff PM, Hannon WH, Khoury MJ. Medium chain acyl-CoA dehydrogenase deficiency human genome epidemiology review. *Genet Med* 1999;1:332-9.
19. Iaifolia AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr* 1994;124:409-15.
20. Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Arch Dis Child* 1994;70:410-2.
21. Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the U.K. *Arch Dis Child* 1998;79:116-9.



22. Zytковicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem* 2001;47:1945-55.
23. Wilcken B, Carpenter K, Wiley V. Comment. *Lancet* 2002;359:627-8.
24. Waisbren SE, Albers S, Amato S, Ampola M, Brewster TG, Demmer L, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. *JAMA* 2003;290:2564-72.
25. Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics* 2002;110:781-6.
26. Venditti LN, Venditti CP, Berry GT, Kaplan PB, Kaye EM, Glick H, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics* 2003;112:1005-15.
27. Meredith-Malloy N, editor. Newborn Screening Quality Assurance Program: 2002 Tandem Mass Spectrometry Annual Summary Report. Atlanta: Centers for Disease Control and Prevention, 2003;2:1-27.
28. American Academy of Pediatrics/Newborn Screening Task Force. Serving the family from birth to medical home. *Pediatrics* 2000;106(suppl):383-427.
29. Pass KA, Lane PA, Fernhoff PM, Hinton CF, Panny SR, Parks JS, et al. U.S. newborn screening system guidelines II: follow-up of children, diagnosis, management, and evaluation. Statement of the Council of Regional Networks for Genetic Services (CORN). *J Pediatr* 2000;137:S1-46.